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Impact of clinical trial findings on Bell's palsy management in the United Kingdom 2001-2012: interrupted time series regression analysis.

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ABSTRACT

Objectives: To measure the incidence of Bell's palsy and determine the impact of clinical trial findings on Bell's palsy management in the UK.

Design: Interrupted time series regression analysis and incidence measures.

Setting: General practices in the United Kingdom contributing to the Clinical Practice Research Datalink (CPRD).

Participants: Patients ≥16 years with a diagnosis of Bell's palsy between 2001 and 2012.

Interventions: 1) Publication of the 2004 Cochrane reviews of clinical trials on corticosteroids and antivirals for Bell's palsy which made no clear recommendation on their use, and 2) publication of the 2007 Scottish Bell's Palsy Study (SBPS) which made a clear recommendation that treatment with prednisolone alone improves chances for complete recovery.

Main Outcome Measures: Incidence of Bell's palsy per 100,000 person-years. Changes in the management of Bell's palsy with either: prednisolone therapy; antiviral therapy; combination therapy (prednisolone with antiviral therapy); or untreated cases.

Results: During the 12 year period 14,460 cases of Bell's palsy were identified with an overall incidence of 37.7 per 100,000 person-years. The 2004 Cochrane reviews were associated with: immediate falls in prednisolone therapy (-6.3% [-11.0 to -1.6]); rising trends in combination therapy (1.1% per quarter [0.5 to 1.7]); and falling trends for untreated cases (-0.8% per quarter [-1.4 to -0.3]). The SBPS was associated with: immediate increases in prednisolone therapy (5.1% [0.9 to 9.3]) and rising trends in prednisolone therapy (0.7% per quarter [0.4 to 1.2]); falling trends in combination therapy (-1.7% per quarter [-2.2 to -1.3]); and rising trends for untreated cases (1.2% per quarter [0.8 to 1.6]). Despite improvements 44.0% still remain untreated.

Conclusions: The SBPS was clearly associated with change in management but a significant proportion of patients failed to receive effective treatment which cannot be fully explained. Clarity and uncertainty in clinical trial recommendations may change clinical practice. However, better ways are needed to understand and circumvent barriers to implementing clinical trial findings.

Article focus

- What is the incidence of Bell's palsy in the UK?
- What has been the impact of clinical trial findings on the management of Bell's palsy?

Key messages

- The incidence of Bell's palsy is 37.7 per 100,000 person years, higher than previously thought.
- Clinical trial findings were clearly associated with change in management
- A significant proportion of Bell's palsy cases still appear to be untreated.

Strengths

- This is the largest population based study evaluating Bell's palsy incidence and management
- The dataset used is of high quality and validated for use in research

Limitations

- Interrupted time series regression assess association rather than causation.
- The reasons for the high proportion of untreated cases remains largely unknown

INTRODUCTION

The foundations of medical evidence are based upon findings from clinical trials but their translation into clinical practice is an uncertain process and can be problematic.[1-3] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which demonstrated an increased risk of cardiovascular events with doxazosin compared to chlorthalidone, was associated with modest but limited reductions in alpha-blocker prescribing in the United States but no immediate impact in other countries.[4, 5] Several theoretical and practical barriers to achieve knowledge translation exist in implementation research and it has been suggested that multi-faceted approaches tailored to the intervention under review are superior to passive dissemination.[6] Two studies assessing the impact of implementing UK National Institute for Clinical Excellence (NICE) guidelines reported variable results suggesting that factors including professional experience, a stable evidence base and cost implications may all influence clinician behaviour.[7, 8] Similar results from a range of clinical settings have been found in other countries.[9-11]

Large population based studies of Bell's palsy (acute idiopathic facial paralysis) are rare and published incidence rates inconsistent, varying from as low as 11 per 100,000 to 51.9 per 100,000 person-years.[12-18] Part of this variation is related to heterogeneity in method of case-detection and diagnostic criteria used. The incidence of Bell's palsy in the UK has been reported only once at 20.2 per 100,000 person-years.[18] However, this measure was based upon electronic health data at a time when electronic medical records (EMRs) were not as widespread or as well integrated into clinical practice as they are now. Currently 97% of UK family doctors use EMRs.[19]

In 2007, the results of a large factorial randomized clinical trial examining the effectiveness of corticosteroids alone or in combination with antivirals for Bell's palsy was reported in the

New England Journal of Medicine.[20] The Scottish Bell's Palsy Study (SBPS) clearly demonstrated that early treatment with prednisolone significantly improved the chance of complete recovery and that treatment with aciclovir conferred no additional benefit. The clinical trial received publicity from other medical journals, evidence-based collections and the general media, raising the profile of the article and helping to disseminate its recommendations.[21, 22] Prior to the SBPS recommendations on the effectiveness of corticosteroids and antivirals for Bell's palsy were unclear.[23, 24] In 2009, a Cochrane review of clinical trials for antivirals in Bell's palsy was published incorporating both the SBPS and data from a large Swedish clinical trial reporting similar findings.[25, 26] The need for high-quality research in this area was therefore demonstrated, large robust clinical trials were conducted, clear recommendations were made and results widely disseminated. In this regard, it would be reasonable to assume changes in clinical practice would then follow. Use of EMRs provides a valuable opportunity to evaluate the impact of clinical trials at a population level and provide robust measures of occurrence. We decided to evaluate the impact of clinical trial data on Bell's palsy management which has never been reported and determine the incidence of Bell's palsy over a twelve year period.

METHODS

The study was conducted using data from the Clinical Practice Research Datalink (CPRD) in the UK, formerly known as the General Practice Research Database.[27] CPRD is one of the world's largest longitudinal databases containing EMRs from over 640 UK general practices. CPRD contains electronic data about patient demographics, prescriptions, clinical events, medical diagnoses, hospital referrals, admissions and deaths. Medical diagnoses and clinical events are recorded using the Read code system of classification.[28] General practices are required to meet defined quality standards in order to contribute data to CPRD which is of high quality having been validated for use in research.[29, 30]

Study population

The study population consisted of all patients ≥16 years of age with an incident diagnosis of Bell's palsy occurring between 1st January 2001 and 30th September 2012. New Bell's palsy cases were defined by an incident Read code for Bell's palsy in patients with at least one year of up to standard medical history. Incidence rates for Bell's palsy were calculated per year and for the overall study period. The numerator was the total number of new Bell's palsy cases recorded by general practitioners and the denominator was the number of person years of total population from contributing practices. Rates per 100,000 person-years were calculated by gender directly standardised to the European standard population.

Outcome

For each new Bell's palsy case, prescription data were used to define four different treatment categories consisting of: oral prednisolone therapy; oral antiviral therapy; oral prednisolone with antiviral (combined) therapy; and untreated. Treatments were defined by prescriptions occurring within seven days of the date of diagnosis. Antiviral therapy was defined by prescriptions for oral acyclovir, famciclovir or valaciclovir. The proportion of

patients treated for Bell's palsy was measured per quarter stratified by treatment category. The denominator used was the total number of new Bell's palsy cases per quarter. Quarters were defined from the beginning of January 2001 (January, February and March) to the end of the third quarter of 2012. For ease of reference quarters are labelled 2001q1 to 2012q3. Referral to secondary care was determined by the presence of a referral code in the primary care records occurring within fourteen days of the date of diagnosis for specialities of: ear, nose and throat (ENT), ophthalmology and neurology. Referral codes were based upon the National Health Service (NHS) classification. Due to limited numbers of referrals, the proportion of Bell's palsy cases referred to secondary care was measured per year.

Events

Events were pre-specified according to publication of the 2004 Cochrane systematic reviews of clinical trials which made no clear recommendation on the use of corticosteroids and antivirals for Bell's palsy (2004q2) [23, 24] and the SBPS which made clear recommendations that treatment with prednisolone alone improved chances of complete recovery (2007q3).[20]

Statistical analysis

Interrupted time series for the specified outcomes were plotted and impact examined in a single segmented regression analysis model with parameters for the two events.[31] Key parameters for each event were estimated: a) the slope or trend in treatment before the event; b) the step change in treatment immediately following the event; and c) the change in trend from the pre-event trend. The presence of serial autocorrelation was tested for using the Durbin-Watson statistic with visual inspection of residuals plots. The minimum number of data points between interventions was thirteen. Associations between untreated cases and the patient characteristics of age and gender were evaluated using multivariate

binary logistic regression. Analysis was conducted using PASW Statistics v18 (IBM Software 2009) and STATAv11 (StataCorp. 2009).

RESULTS

Incidence of Bell's palsy

A total of 14,460 patients with incident Bell's palsy were identified (table 1). The overall incidence of Bell's palsy for the study period was 37.7 per 100,000 person-years. The incidence of Bell's palsy increased with age and was similar for gender. The annual standardised incidence of Bell's palsy remained fairly constant throughout the period of study (figure 1).

Effect of clinical trials on management

Time trends for the management of Bell's palsy are shown in figure 2. In 2001q1 Bell's palsy was treated with prednisolone only in 33.4% (95%CI 29.8-37.0); combined therapy in 5.1% (95%CI 1.7 to 8.5); antivirals only in 1.1% (95%CI -0.1 to 2.3); and was untreated in 60.4% (95%CI 57.1 to 63.8). The baseline trend was flat for all treatment categories i.e. there were no significant quarter to quarter changes in treatment (table 2). The 2004 Cochrane systematic reviews of clinical trials were associated with; a significant absolute step fall in treatment with prednisolone of -6.3% (95%CI -11.0 to -1.6) during 2004q2 without any significant change in trend; change from a flat to a significantly rising trend in treatment with combined therapy of 1.1% per quarter (95%CI 0.5 to 1.7); and change from a flat to a significantly falling trend in untreated patients (-0.8% per quarter [95%CI -1.4 to -0.3]). The SBPS was associated with: a significant immediate step rise in treatment with prednisolone only of 5.1% (95%CI 0.9 to 9.3) followed by a rising trend of 0.7% per quarter (95%CI 0.4 to 1.2); change from a rising to a falling trend in treatment with combined

therapy of -1.7% per quarter (95%CI -2.2 to -1.3); change from a falling to a rising trend in untreated patients (1.0% per quarter [95%CI 0.2 to 1.9]); and change to a falling trend in treatment with antivirals alone (-0.2% per quarter [95%CI -0.4 to -0.0]).

Untreated cases

The proportion of untreated Bell's palsy patients fell from 62% during the 12 year study period but remained at 44.0% at 2012q3. The proportion of untreated Bell's palsy patients was high across all age categories (range 44.4% to 58.0%, table 3) but was significantly greater in patients over the age of 60 years. The probability of being untreated was not significantly influenced by gender.

Referrals to secondary care

Of the 14,460 new Bell's palsy cases identified, a total of 1051 (7.3%, 95%CI 6.9 to 7.7) patients were referred to ENT, ophthalmology or neurology. More treated cases of Bell's palsy were referred to secondary care than untreated cases (9.2% [95%CI 8.5 to 9.9] for treated vs. 6.5% [95%CI 5.9 to 7.1] for untreated). The proportion of patients referred to secondary care fell during the study period (figure 3) ranging from 9.2% (95%CI 7.5 to 11.2) in the first quarter of 2001 to 5.9% (95%CI 4.6 to 7.6) in the third quarter of 2012 (difference 3.3%, 95%CI -0.1 to 6.6%).

DISCUSSION

Clinical trial findings are the cornerstone of medical evidence to judge the effectiveness of interventions but not all recommendations effectively translate into clinical practice. Evaluating changes in prescribing behaviour at a population level can support clinical trials in measuring their impact.

Impact of clinical trial evidence

The SBPS was associated with a significant clinical impact on Bell's palsy management by increasing treatment with corticosteroids and reducing combination therapy with antivirals. In this sense, use of corticosteroids increased by 88% from the lowest point in 2005 to the highest in 2010. Conversely, combination therapy fell by 41% from the highest point in 2007 to the lowest in 2010. Equally important however, uncertainty in recommendation or lack of evidence from clinical trials also appears to significantly influence clinical practice. This is highlighted by the 2004 reviews which were associated with an increase in combination therapy by 323% from the lowest point in 2004 to the highest in 2007. There are several reasons why this may have occurred. Clinical uncertainties regarding effectiveness may have justified the use of antivirals with increasing pharmaceutical promotion. This would also indirectly promote corticosteroid use and help explain the falling trend in untreated patients. When no evidence for antivirals was found, promotion of combination therapy for Bell's palsy may have stopped, thus halting the falling trend in untreated patients. Corticosteroids being off-patent cheap drugs were unlikely to be marketed in the same way. Uncertainty in clinical management partly stems from uncertainty regarding aetiology. If a non-viral aetiology for Bell's palsy was confirmed, the use of antiviral would be biologically implausible. Further work could usefully address the aetiology of Bell's palsy.

Adoption of clinical trial findings from the SBPS clearly occurred but was limited despite clear recommendations and subsequent dissemination. In this regard, a significant number of patients are still treated with antivirals and even more receive no effective treatment despite updated recommendations.[26, 32] This may be related to conflicting recommendations for antiviral use appearing in the literature after the SBPS, especially in relation to severe cases.[33-35] These uncertainties make recommendations less likely to be adopted.[10]

Untreated cases

Significant numbers of patients failed to receive effective therapy for Bell's palsy. Increasing age is associated with increasing co-morbidity, which may lead to relative contraindications to therapy. Although older patients had the greatest probability of being untreated, the proportion of untreated patients was high among all age categories with 44.4% of patients under the age of 30 appearing to not receive any effective treatment by the end of the study period. It is therefore likely that relative contraindications to therapy as a result of co-morbidities would account for only a minority of untreated cases. In older patients, the main differential diagnosis of Bell's palsy is stroke which may have resulted in more patients receiving treatment from secondary care services. In this regard, cases may have presented to accident and emergency rather than primary care as a result of recommendations for rapid urgent assessment of suspected stroke leading to an overestimate in the number of untreated patients in this age category.[36] Conversely, concerns regarding a diagnosis of stroke may also lead to delayed diagnosis of Bell's palsy potentially missing the opportunity for early effective treatment with prednisolone therapy in these patients.

Incidence

The incidence of Bell's palsy was similar between genders, increased with age and remained fairly constant throughout the twelve year period. The incidence of Bell's palsy varies markedly throughout the literature with differences partly relating to the method of case-detection or diagnostic criteria used. Although the incidence of Bell's palsy in this study was greater than for others [14, 15, 17, 18] a large US study using electronic health surveillance data reported a similar incidence of 42.7 per 100,000 person-years.[16] Our study also reported similar increases in incidence with age found elsewhere.[16, 18]

Given the low rate of referrals to ENT, ophthalmology and neurology specialities (the main specialities patients with Bell's palsy would be referred to in the UK) it can be seen that primary care physicians diagnose and treat the great majority of cases. For the UK at least, primary care data are therefore a valuable source for measuring the incidence of Bell's palsy. Only one other study has reported incidence rates from the UK. Rowlands et al used EMRs from 1992 to 1996 to estimate an incidence of 20 per 100,000 person-years, a figure significantly lower than ours.[18] It remains uncertain whether the incidence of Bell's palsy has truly increased or simply been measured more accurately. The previous study used data at a time when EMRs and established coding practices were not as widespread or as well integrated into clinical practice as they are now which may have led to an under-recording of cases. The fairly stable trend in incidence over a twelve year period from our study also makes it less likely that the incidence of Bell's palsy has increased over time.

Strengths and limitations

This is the largest population based study evaluating the incidence and management of Bell's palsy. Perhaps of greater importance however lies in demonstrating the impact of clinical trials on Bell's palsy management, which has never been reported potentially having

wider implications. Cochrane systematic reviews are considered a gold standard for summaries of evidence-based healthcare in the UK and internationally because of the rigorous approach in combining high-standard medical research. For this reason the Cochrane systematic reviews of clinical trials were evaluated especially as changes in recommendation occurred during the study period. In the UK, patients register with general practices in order to access free healthcare from the NHS. Most prescriptions, including those recommended from secondary care, are issued electronically from general practice making UK EMRs a valuable tool for research. Bell's palsy cases were diagnosed by family physicians in real life settings and no scale was used to quantify the degree of facial nerve dysfunction. Some patients may have received treatment from other sources (e.g. accident and emergency units) with potential overestimation of untreated patients. However, this is likely to be a minority of patients due to the culture of healthcare provision in the UK and the size and quality of the database used. Time series regression assesses association rather than causation but remains a strong design for estimating the effects of interventions in non-randomized settings.[29] Despite this, we cannot exclude the possibility that other events may have occurred which influenced the findings.

Clinical implications

A large proportion of patients do not appear to receive any effective treatment for their condition. Although most Bell's palsy cases will resolve spontaneously, full recovery is more likely and quicker in those treated with prednisolone. This is important as around 30% of untreated patients will suffer long term problems including facial disfigurement potentially complicated by facial contracture, reduced sense of taste, speech problems, eye-mouth synkinesias, corneal ulceration and adverse psychological impact. Clearly, any treatment which reduces the risk of long-term complications and speeds up recovery should be

considered. Therefore, more people should be offered early treatment with corticosteroids for Bell's palsy. More broadly, there is a societal need in health care research to better evaluate the impact of large clinical trials and not to assume that knowledge translation naturally occurs via passive dissemination. More work is therefore needed to understand and circumvent the barriers to adoption of clinical trial evidence. In conclusion, clinical trial findings had a clear impact on primary care management of Bell's palsy but a significant proportion of patients failed to receive effective treatment. Clinical trials making clear recommendations can be associated with changes to clinical practice, but their impact may still be limited. Conversely, lack of evidence or uncertain clinical trial recommendations may also be associated with changes in clinical practice. Better ways are needed to circumvent the barriers to implementing clinical trial results.

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Ethical approval: The study was approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC).

Data sharing: Descriptive statistics for Bell's palsy cases are available from the corresponding author.

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TABLES

Table 1. Incidence of Bell's palsy (per 100,000 person-years) by age and gender.

Age (years)	Male		Female		Overall Incidence
	No. (%)	Incidence*	No. (%)	Incidence*	
16-30	949 (46.2)	24.0	1107 (53.8)	30.3	27.0
30-39	1155 (49.2)	33.6	1194 (50.8)	35.6	34.5
40-49	1313 (52.2)	34.4	1202 (47.8)	32.5	33.4
50-59	1341 (52.0)	40.0	1237 (48.0)	37.6	38.8
60-69	1229 (51.0)	45.9	1180 (49.0)	42.9	44.4
≥70	1154 (45.2)	66.6	1399 (54.8)	68.2	67.4

Table 2. Quarterly time series regression analysis of Bell's palsy treatment from 2001 to 2012.

Event	Segments*	Untreated % (95% CI)	Prednisolone % (95% CI)	Combination % (95% CI)	Antiviral % (95% CI)
Baseline	2001q1 (intercept)	60.43 (57.10 to 63.78)	33.39 (29.79 to 36.99)	5.10 (1.78 to 8.42)	1.09 (-0.09 to 2.26)
1	2001q1 to 2004q1	-0.28 (-0.69 to 0.13)	-0.01 (-0.47 to 0.44)	0.18 (-0.24 to 0.60)	0.11 (-0.04 to 0.27)
	20004q2 step change	2.15 (-2.15 to 6.44)	-6.32 (-11.03 to -1.60)	3.61 (-0.74 to 7.96)	0.57 (-1.05 to 2.18)
	2004q2 to 2007q3	-0.81 (-1.36 to -0.25)	-0.27 (-0.88 to 0.34)	1.09 (0.53 to 1.65)	-0.01 (-0.22 to 0.20)
2	2007q4 step change	-2.13 (-5.96 to 1.70)	5.10 (0.90 to 9.31)	-2.17 (-6.05 to 1.72)	-0.81 (-2.25 to 0.63)
	2007q4 to 20012q3	1.22 (0.79 to 1.64)	0.71 (0.41 to 1.18)	-1.73 (-2.17 to -1.30)	-0.19 (-0.35 to -0.03)
Final	2012q3	43.98 (38.02 to 49.94)	33.83 (28.15 to 39.51)	18.42 (13.76 to 23.08)	3.76 (1.47 to 6.05)

*Trend in prescribing before and after the event including step changes. Significantly rising or falling trends underlined.

1= 2004 Cochrane systematic reviews of clinical trials on corticosteroids and aciclovir or valaciclovir for Bell's palsy [3,4].

2= 2007 Scottish Bell's palsy study [5].

Final= percentage of patients treated for Bell's palsy at the end of the study period according to the categories of treatment.

Table 3. Untreated cases according to age and gender with results from multivariate logistic regression analysis.

Variable		Untreated (%)	Odds ratio (95%CI)	*P* value
Age group	16-30	913 (44.4)	-	
	30-39	1105 (47.0)	1.11 (0.99-1.25)	0.077
	40-49	1157 (46.0)	1.07 (0.95-1.20)	0.263
	50-59	1225 (47.6)	1.14 (1.01-1.28)	0.032
	60-69	1215 (50.4)	1.28 (1.13-1.44)	<0.001
	>70	1480 (58.0)	1.73 (1.54-1.94)	<0.001
Gender	Male	3459 (48.4)	-	
	Female	3636 (49.7)	1.04 (0.98-1.11)	0.231

FIGURE LEGENDS

Figure 1. Incidence of Bell's palsy in the UK from 2001 to 2012, standardised to the European standard population.

Error bars = 95% confidence intervals.

Figure 2. Management of Bell's palsy in the UK according to treatment.

Reference line: 1 = the 2004 Cochrane systematic reviews for Bell's palsy.

Reference line 2 = the 2007 SBPS.

Figure 3. Trends in referral to secondary care for Bell's palsy in the UK from 2001 to 2012.

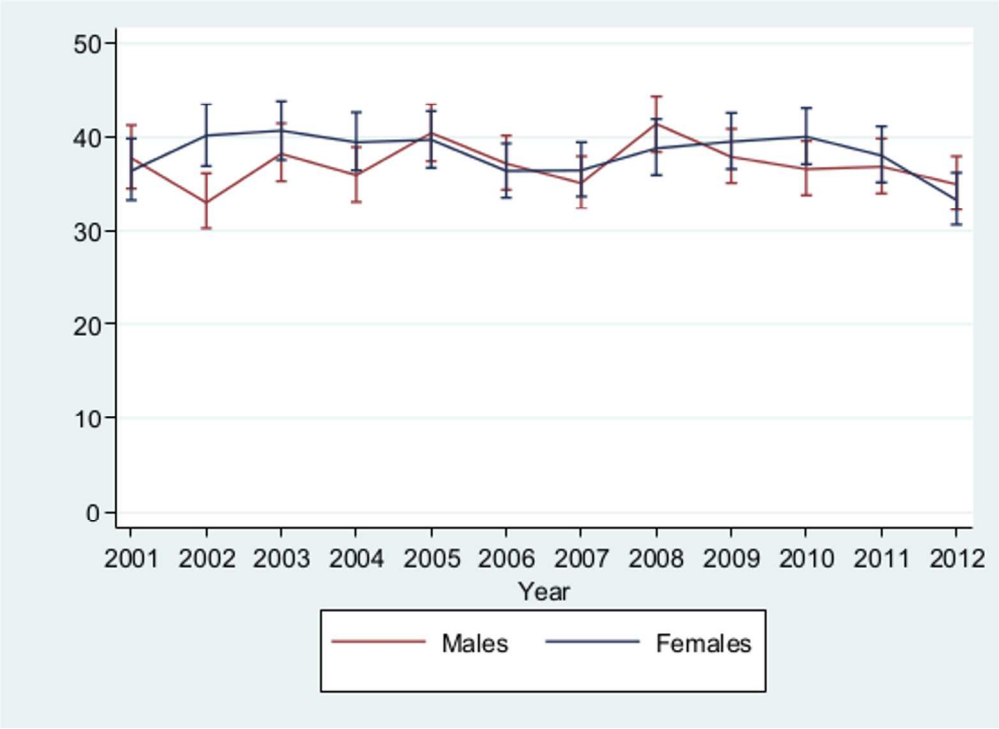

Figure 1. Incidence of Bell's palsy in the UK from 2001 to 2012, standardised to the European standard population.
Error bars = 95% confidence intervals.

173x125mm (300 x 300 DPI)

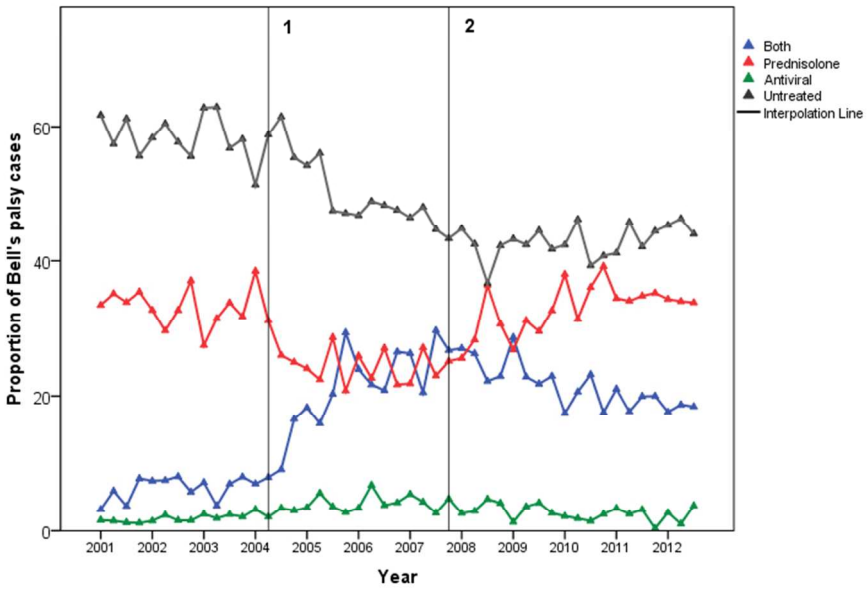

Figure 2. Management of Bell's palsy in the UK according to treatment.
Reference line: 1 = the 2004 Cochrane systematic reviews for Bell's palsy.
Reference line 2 = the 2007 SBPS.

288x190mm (72 x 72 DPI)

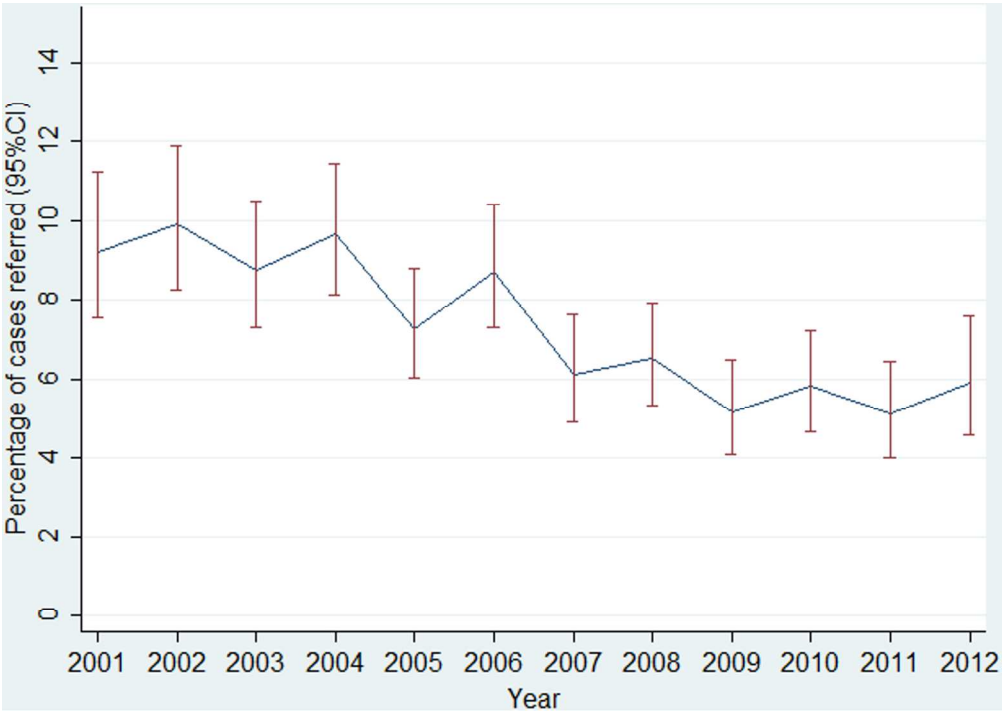

Figure 3. Trends in referral to secondary care for Bell's palsy in the UK from 2001 to 2012.
173x122mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page4
Methods			
Study design	4	Present key elements of study design early in the paper	Page5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page5-6
Bias	9	Describe any efforts to address potential sources of bias	Page5
Study size	10	Explain how the study size was arrived at	Page6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page6-7
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page7-8 Table 1
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1&3
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Page7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Table2

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Page7-8 Table2,3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Impact of clinical trial findings on Bell's palsy management in General Practice in the United Kingdom 2001-2012: interrupted time series regression analysis.

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Impact of clinical trial findings on Bell's palsy management in General Practice in the United Kingdom 2001-2012: interrupted time series regression analysis.

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ABSTRACT

Objectives: To measure the incidence of Bell's palsy and determine the impact of clinical trial findings on Bell's palsy management in the UK.

Design: Interrupted time series regression analysis and incidence measures.

Setting: General practices in the United Kingdom contributing to the Clinical Practice Research Datalink (CPRD).

Participants: Patients ≥16 years with a diagnosis of Bell's palsy between 2001 and 2012.

Interventions: 1) Publication of the 2004 Cochrane reviews of clinical trials on corticosteroids and antivirals for Bell's palsy which made no clear recommendation on their use, and 2) publication of the 2007 Scottish Bell's Palsy Study (SBPS) which made a clear recommendation that treatment with prednisolone alone improves chances for complete recovery.

Main Outcome Measures: Incidence of Bell's palsy per 100,000 person-years. Changes in the management of Bell's palsy with either: prednisolone therapy; antiviral therapy; combination therapy (prednisolone with antiviral therapy); or untreated cases.

Results: During the 12 year period 14,460 cases of Bell's palsy were identified with an overall incidence of 37.7 per 100,000 person-years. The 2004 Cochrane reviews were associated with: immediate falls in prednisolone therapy (-6.3% [-11.0 to -1.6]); rising trends in combination therapy (1.1% per quarter [0.5 to 1.7]); and falling trends for untreated cases (-0.8% per quarter [-1.4 to -0.3]). The SBPS was associated with: immediate increases in prednisolone therapy (5.1% [0.9 to 9.3]) and rising trends in prednisolone therapy (0.7% per quarter [0.4 to 1.2]); falling trends in combination therapy (-1.7% per quarter [-2.2 to -1.3]); and rising trends for untreated cases (1.2% per quarter [0.8 to 1.6]). Despite improvements 44.0% still remain untreated.

Conclusions: The SBPS was clearly associated with change in management but a significant proportion of patients failed to receive effective treatment which cannot be fully explained. Clarity and uncertainty in clinical trial recommendations may change clinical practice. However, better ways are needed to understand and circumvent barriers to implementing clinical trial findings.

Article focus

- What is the incidence of Bell's palsy in people aged 16 years onwards in the UK?
- What has been the impact of clinical trial findings on the management of Bell's palsy?

Key messages

- The incidence of Bell's palsy is 37.7 per 100,000 person years, higher than previously thought.
- Clinical trial findings were clearly associated with change in management
- A significant proportion of Bell's palsy cases still appear to be untreated.

Strengths

- This is the largest population based study evaluating Bell's palsy incidence and management
- The dataset used is of high quality and validated for use in research

Limitations

- Interrupted time series regression assess association rather than causation.
- The reasons for the high proportion of untreated cases remains largely unknown

INTRODUCTION

The foundations of medical evidence are based upon findings from clinical trials but their translation into clinical practice is an uncertain process and can be problematic.[1-3] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which demonstrated an increased risk of cardiovascular events with doxazosin compared to chlorthalidone, was associated with modest but limited reductions in alpha-blocker prescribing in the United States but no immediate impact in other countries.[4, 5] Several theoretical and practical barriers to achieve knowledge translation exist in implementation research and it has been suggested that multi-faceted approaches tailored to the intervention under review are superior to passive dissemination.[6] Two studies assessing the impact of implementing UK National Institute for Clinical Excellence (NICE) guidelines reported variable results suggesting that factors including professional experience, a stable evidence base and cost implications may all influence clinician behaviour.[7, 8] Similar results from a range of clinical settings have been found in other countries.[9-11]

Large population based studies measuring the incidence of Bell's palsy (acute idiopathic facial palsy) are rare. Currently published incidence rates of Bell's palsy are inconsistent, varying from as low as 11 per 100,000 to 51.9 per 100,000 person-years.[12-18] Part of this variation is related to heterogeneity in the method of case-detection and differences in diagnostic criteria used. In addition, not all published studies are large population based studies and variations in sampling technique may bias measures of disease occurrence. The incidence of Bell's palsy in the UK has been reported only once at 20.2 per 100,000 person-years.[18] However, this measure was based upon electronic health data at a time when electronic medical records (EMRs) were not as widespread or as well integrated into clinical practice as they are now. Currently 97% of UK family doctors use EMRs.[19]

In 2007, the results of a large factorial randomized clinical trial examining the effectiveness of corticosteroids alone or in combination with antivirals for Bell's palsy was reported in the New England Journal of Medicine.[20] The Scottish Bell's Palsy Study (SBPS) clearly demonstrated that early treatment with prednisolone significantly improved the chance of complete recovery and that treatment with aciclovir conferred no additional benefit. The clinical trial received publicity from other medical journals, evidence-based collections and the general media, raising the profile of the article and helping to disseminate its recommendations.[21, 22] Prior to the SBPS recommendations on the effectiveness of corticosteroids and antivirals for Bell's palsy were unclear.[23, 24] In 2009, a Cochrane review of clinical trials for antivirals in Bell's palsy was published incorporating both the SBPS and data from a large Swedish clinical trial reporting similar findings.[25, 26] The need for high-quality research in this area was therefore demonstrated, large robust clinical trials were conducted, clear recommendations were made and results widely disseminated. In this regard, it would be reasonable to assume changes in clinical practice would then follow. Use of EMRs provides a valuable opportunity to evaluate the impact of clinical trials at a population level and provide robust measures of occurrence. We decided to evaluate the impact of clinical trial data on Bell's palsy management which has never been reported and determine the incidence of Bell's palsy over a twelve year period.

METHODS

The study was conducted using data from the Clinical Practice Research Datalink (CPRD) in the UK, formerly known as the General Practice Research Database.[27] CPRD is one of the world's largest longitudinal databases containing EMRs from over 640 UK general practices. CPRD contains electronic data about patient demographics, prescriptions, clinical events, medical diagnoses, hospital referrals, admissions and deaths. Medical diagnoses and clinical events are recorded using the Read code system of classification.[28] General practices are required to meet defined quality standards in order to contribute data to CPRD which is of high quality having been validated for use in research.[29, 30]

Study population

The study population consisted of all patients ≥16 years of age with an incident diagnosis of Bell's palsy occurring between 1st January 2001 and 30th September 2012. New Bell's palsy cases were defined by an incident Read code for Bell's palsy in patients with at least one year of up to standard medical history before the incident Read code for Bell's palsy. Incidence rates for Bell's palsy were calculated per year and for the overall study period. The numerator was the total number of new Bell's palsy cases recorded by general practitioners and the denominator was the number of person years of total population from contributing practices. Rates per 100,000 person-years were calculated by gender directly standardised to the European standard population.

Outcome

For each new Bell's palsy case, prescription data were used to define four different treatment categories consisting of: oral prednisolone therapy; oral antiviral therapy; oral prednisolone with antiviral (combined) therapy; and untreated. Treatments were defined by prescriptions occurring within seven days before and after the date of diagnosis. Antiviral

therapy was defined by prescriptions for oral acyclovir, famciclovir or valaciclovir. The proportion of patients treated for Bell's palsy was measured per quarter stratified by treatment category. The denominator used was the total number of new Bell's palsy cases per quarter. Quarters were defined from the beginning of January 2001 (January, February and March) to the end of the third quarter of 2012. For ease of reference quarters are labelled 2001q1 to 2012q3. Referral to secondary care was determined by the presence of a referral code in the primary care records occurring within fourteen days of the date of diagnosis for specialities of: ear, nose and throat (ENT), ophthalmology and neurology. Referral codes were based upon the National Health Service (NHS) classification. Due to limited numbers of referrals, the proportion of Bell's palsy cases referred to secondary care was measured per year.

Events

Events were pre-specified according to publication of the 2004 Cochrane systematic reviews of clinical trials which made no clear recommendation on the use of corticosteroids and antivirals for Bell's palsy (2004q2) [23, 24] and the SBPS which made clear recommendations that treatment with prednisolone alone improved chances of complete recovery (2007q3).[20]

Statistical analysis

Interrupted time series for the specified outcomes were plotted and impact examined in a single segmented regression analysis model with parameters for the two events.[31] Key parameters for each event were estimated: a) the slope or trend in treatment before the event; b) the step change in treatment immediately following the event; and c) the change in trend from the pre-event trend. The presence of serial autocorrelation was tested for using the Durbin-Watson statistic with visual inspection of residuals plots. The minimum

number of data points between interventions was thirteen. Associations between untreated cases and the patient characteristics of age and gender were evaluated using multivariate binary logistic regression. Analysis was conducted using PASW Statistics v18 (IBM Software 2009) and STATAv11 (StataCorp. 2009).

RESULTS

Incidence of Bell's palsy

A total of 14,460 patients with incident Bell's palsy were identified (table 1). The overall incidence of Bell's palsy for the study period was 37.7 per 100,000 person-years. The incidence of Bell's palsy increased with age and was similar for gender. The annual standardised incidence of Bell's palsy remained fairly constant throughout the period of study (figure 1).

Effect of clinical trials on management

Time trends for the management of Bell's palsy are shown in figure 2. In 2001q1 Bell's palsy was treated with prednisolone only in 33.4% (95%CI 29.8-37.0); combined therapy in 5.1% (95%CI 1.7 to 8.5); antivirals only in 1.1% (95%CI -0.1 to 2.3); and was untreated in 60.4% (95%CI 57.1 to 63.8). The baseline trend was flat for all treatment categories i.e. there were no significant quarter to quarter changes in treatment (table 2). The 2004 Cochrane systematic reviews of clinical trials were associated with; a significant absolute step fall in treatment with prednisolone of -6.3% (95%CI -11.0 to -1.6) during 2004q2 without any significant change in trend; change from a flat to a significantly rising trend in treatment with combined therapy of 1.1% per quarter (95%CI 0.5 to 1.7); and change from a flat to a significantly falling trend in untreated patients (-0.8% per quarter [95%CI -1.4 to -0.3]).

The SBPS was associated with: a significant immediate step rise in treatment with prednisolone only of 5.1% (95%CI 0.9 to 9.3) followed by a rising trend of 0.7% per quarter (95%CI 0.4 to 1.2); change from a rising to a falling trend in treatment with combined therapy of -1.7% per quarter (95%CI -2.2 to -1.3); change from a falling to a rising trend in untreated patients (1.0% per quarter [95%CI 0.2 to 1.9]); and change to a falling trend in treatment with antivirals alone (-0.2% per quarter [95%CI -0.4 to -0.0]).

Untreated cases

The proportion of untreated Bell's palsy patients fell from 62% during the 12 year study period but remained at 44.0% at 2012q3. The proportion of untreated Bell's palsy patients was high across all age categories (range 44.4% to 58.0%, table 3) but was significantly greater in patients over the age of 60 years. The probability of being untreated was not significantly influenced by gender.

Referrals to secondary care

Of the 14,460 new Bell's palsy cases identified, a total of 1051 (7.3%, 95%CI 6.9 to 7.7) patients were referred to ENT, ophthalmology or neurology. More treated cases of Bell's palsy were referred to secondary care than untreated cases (9.2% [95%CI 8.5 to 9.9] for treated vs. 6.5% [95%CI 5.9 to 7.1] for untreated). The proportion of patients referred to secondary care fell during the study period (figure 3) ranging from 9.2% (95%CI 7.5 to 11.2) in the first quarter of 2001 to 5.9% (95%CI 4.6 to 7.6) in the third quarter of 2012 (difference 3.3%, 95%CI -0.1 to 6.6%).

DISCUSSION

Clinical trial findings are the cornerstone of medical evidence to judge the effectiveness of interventions but not all recommendations effectively translate into clinical practice. Evaluating changes in prescribing behaviour at a population level can support clinical trials in measuring their impact.

Impact of clinical trial evidence

The SBPS was associated with a significant clinical impact on Bell's palsy management by increasing treatment with corticosteroids and reducing combination therapy with antivirals based upon the results of time series regression analysis. Use of prednisolone alone increased by 70% from the point immediately before publication of the SBPS to the highest point in 2010. Conversely, combination therapy fell by 41% from the point immediately before publication of the SBPS to the lowest point in 2010. Equally important however, uncertainty in recommendation or lack of evidence from clinical trials also appears to significantly influence clinical practice. This is highlighted by the 2004 reviews which were associated with an increase in combination therapy by 323% from the lowest point in 2004 to the highest point in 2007. There are several reasons why this may have occurred. Clinical uncertainties regarding effectiveness may have justified the use of antivirals with increasing pharmaceutical promotion. This would also indirectly promote corticosteroid use and help explain the falling trend in untreated patients. When no evidence for antivirals was found, promotion of combination therapy for Bell's palsy may have stopped, thus halting the falling trend in untreated patients. Corticosteroids being off-patent cheap drugs were unlikely to be marketed in the same way. Uncertainty in clinical management partly stems from uncertainty regarding aetiology. If a non-viral aetiology for Bell's palsy was confirmed, the

use of antiviral would be biologically implausible. Further work could usefully address the aetiology of Bell's palsy.

Adoption of clinical trial findings from the SBPS clearly occurred but was limited despite clear recommendations and subsequent dissemination. In this regard, a significant number of patients are still treated with antivirals and even more receive no effective treatment despite updated recommendations.[26, 32] In addition, there is a suggestion that the rising trend in prednisolone only therapy and falling trend in combination therapy over the last year of observation is plateauing, which may be an effect related to the time since publication. This may be related to conflicting recommendations for antiviral use appearing in the literature after the SBPS, especially in relation to severe cases.[33-35] These uncertainties make recommendations less likely to be adopted.[10] Relatively few studies have attempted to evaluate the impact of clinical trials on clinical practice. The ALLHAT trial was a large randomised double-blind trial in which the study doxazosin arm was terminated early due to an unfavourable risk of cardiovascular events compared to treatment with chlorthalidone. The ALLHAT trial was associated with a 26% reduction in annual alpha-blocker prescription orders, a 22% reduction in dispensed alpha-blocker prescriptions and a 54% reduction in physician reported alpha-blocker drug-use in the US.[4] Despite the clinically significant reductions, significant numbers of hypertensive patients still received treatment with alpha-blockade and it was proposed that further strategies are required to increase the impact clinical trial findings should have. Our study observed similar findings in that although a clinically significant impact occurred, clinical evidence was not fully adopted.

Untreated cases

Significant numbers of patients failed to receive effective therapy for Bell's palsy. Increasing age is associated with increasing co-morbidity, which may lead to relative contraindications to therapy. Although older patients had the greatest probability of being untreated, the proportion of untreated patients was high among all age categories with 44.4% of patients

under the age of 30 appearing to not receive any effective treatment by the end of the study period. It is therefore likely that relative contraindications to therapy as a result of co-morbidities would account for only a minority of untreated cases. In older patients, the main differential diagnosis of Bell's palsy is stroke which may have resulted in more patients receiving investigation and treatment from secondary care services. In this regard, cases may have presented to accident and emergency rather than primary care as a result of recommendations for rapid urgent assessment of suspected stroke potentially overestimating the number of untreated patients in this age category. Conversely, concerns regarding a diagnosis of stroke may also lead to delayed diagnosis of Bell's palsy potentially missing the opportunity for early effective treatment with prednisolone therapy in these patients.

Incidence

The incidence of Bell's palsy was similar between genders, increased with age and remained fairly constant throughout the twelve year period. The incidence of Bell's palsy varies markedly throughout the literature with differences partly relating to the method of case-detection or diagnostic criteria used. Although the incidence of Bell's palsy in this study was greater than for others [14, 15, 17, 18] a large US study using electronic health surveillance data reported a similar incidence of 42.7 per 100,000 person-years.[16] Our study also reported similar increases in incidence with age found elsewhere.[16, 18]

Given the low rate of referrals to ENT, ophthalmology and neurology specialities (the main specialities patients with Bell's palsy would be referred to in the UK) it can be seen that primary care physicians diagnose and treat the great majority of cases. For the UK at least, primary care data are therefore a valuable source for measuring the incidence of Bell's palsy. Only one other study has reported incidence rates from the UK. Rowlands et al used

EMRs from 1992 to 1996 to estimate an incidence of 20 per 100,000 person-years, a figure significantly lower than ours.[18] It remains uncertain whether the incidence of Bell's palsy has truly increased or simply been measured more accurately. The previous study used data at a time when EMRs and established coding practices were not as widespread or as well integrated into clinical practice as they are now which may have led to an under-recording of cases. The fairly stable trend in incidence over a twelve year period from our study also makes it less likely that the incidence of Bell's palsy has increased over time.

Strengths and limitations

This is the largest population based study evaluating the incidence and management of Bell's palsy in adults. Bell's palsy may occur rarely in children however the vast majority of cases will occur in adults and increases substantially with age. Acute idiopathic facial palsy in children is more likely to be managed in secondary care, from which no prescribing data are available. As such, inclusion of patients assessing the impact of clinical trial data would be to underestimate the impact of clinical trial findings. Perhaps of greater importance however lies in demonstrating the impact of clinical trials on Bell's palsy management, which has never been reported potentially having wider implications. Cochrane systematic reviews are considered a gold standard for summaries of evidence-based healthcare in the UK and internationally because of the rigorous approach in combining high-standard medical research. For this reason the Cochrane systematic reviews of clinical trials were evaluated especially as changes in recommendation occurred during the study period. In the UK, patients register with general practices in order to access free healthcare from the NHS. Most prescriptions, including those recommended from secondary care, are issued electronically from general practice making UK EMRs a valuable tool for research. Bell's palsy cases were diagnosed by family physicians in real life settings and no scale was used to

quantify the degree of facial nerve dysfunction. We are unable to ascertain whether or not the diagnosis of Bell's palsy was recorded at initial presentation or following complete investigation. For this reason, we included prescriptions issued within a seven day period before and after the date of Bell's palsy recording. Some patients may have received treatment from other sources (e.g. accident and emergency units) with potential overestimation of untreated patients. However, this is likely to be a minority of patients due to the culture of healthcare provision in the UK and the size and quality of the database used. Although it would appear from the low rate of referrals to ophthalmology, ENT and neurology that Bell's palsy is primarily managed in primary care, we cannot exclude the possibility that patients were referred to other disciplines potentially underestimating the number of referrals. Time series regression assesses association rather than causation but remains a strong design for estimating the effects of interventions in non-randomized settings.[29] Despite this, we cannot exclude the possibility that other events may have occurred which influenced the findings.

Clinical implications

A large proportion of patients do not appear to receive any effective treatment for their condition. Although the majority of Bell's palsy cases will resolve spontaneously, full recovery is more likely and quicker in those treated with prednisolone.[20,36] This is important as around 30% of untreated patients will suffer long term problems including facial disfigurement potentially complicated by facial contracture, reduced sense of taste, speech problems, eye-mouth synkinesias, corneal ulceration and adverse psychological impact. Clearly, any treatment which reduces the risk of long-term complications and speeds up recovery should be considered. Therefore, more people should be offered early treatment with corticosteroids for Bell's palsy. More broadly, there is a societal need in

health care research to better evaluate the impact of large clinical trials and not to assume that knowledge translation naturally occurs via passive dissemination. More work is therefore needed to understand and circumvent the barriers to adoption of clinical trial evidence. In conclusion, clinical trial findings had a clear impact on primary care management of Bell's palsy but a significant proportion of patients failed to receive effective treatment. Clinical trials making clear recommendations can be associated with changes to clinical practice, but their impact may still be limited. Conversely, lack of evidence or uncertain clinical trial recommendations may also be associated with changes in clinical practice. Better ways are needed to circumvent the barriers to implementing clinical trial results.

Contributors: FS and FD had the original idea for this study. DM and PD contributed to the development of the idea and the study design. DM and PD and undertook the primary analysis. TS obtained the data and contributed to the design and interpretation. DM and FS wrote the first draft of the paper. FD, PD and TS critically reviewed the paper. DM is guarantor. All authors approved the submitted version.

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Ethical approval: The study was approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC).

Data sharing: Descriptive statistics for Bell's palsy cases are available from the corresponding author.

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TABLES

Table 1. Incidence of Bell's palsy (per 100,000 person-years) by age and gender.

Age (years)	Male		Female		Overall Incidence
	No. (%)	Incidence*	No. (%)	Incidence*	
16-30	949 (46.2)	24.0	1107 (53.8)	30.3	27.0
30-39	1155 (49.2)	33.6	1194 (50.8)	35.6	34.5
40-49	1313 (52.2)	34.4	1202 (47.8)	32.5	33.4
50-59	1341 (52.0)	40.0	1237 (48.0)	37.6	38.8
60-69	1229 (51.0)	45.9	1180 (49.0)	42.9	44.4
≥70	1154 (45.2)	66.6	1399 (54.8)	68.2	67.4

Table 2. Quarterly time series regression analysis of Bell's palsy treatment from 2001 to 2012.

Event	Segments*	Untreated % (95% CI)	Prednisolone % (95% CI)	Combination % (95% CI)	Antiviral % (95% CI)
Baseline	2001q1 (intercept)	60.43 (57.10 to 63.78)	33.39 (29.79 to 36.99)	5.10 (1.78 to 8.42)	1.09 (-0.09 to 2.26)
1	2001q1 to 2004q1	-0.28 (-0.69 to 0.13)	-0.01 (-0.47 to 0.44)	0.18 (-0.24 to 0.60)	0.11 (-0.04 to 0.27)
	20004q2 step change	2.15 (-2.15 to 6.44)	-6.32 (-11.03 to -1.60)	3.61 (-0.74 to 7.96)	0.57 (-1.05 to 2.18)
	2004q2 to 2007q3	-0.81 (-1.36 to -0.25)	-0.27 (-0.88 to 0.34)	1.09 (0.53 to 1.65)	-0.01 (-0.22 to 0.20)
2	2007q4 step change	-2.13 (-5.96 to 1.70)	5.10 (0.90 to 9.31)	-2.17 (-6.05 to 1.72)	-0.81 (-2.25 to 0.63)
	2007q4 to 20012q3	1.22 (0.79 to 1.64)	0.71 (0.41 to 1.18)	-1.73 (-2.17 to -1.30)	-0.19 (-0.35 to -0.03)
Final	2012q3	43.98 (38.02 to 49.94)	33.83 (28.15 to 39.51)	18.42 (13.76 to 23.08)	3.76 (1.47 to 6.05)

*Trend in prescribing before and after the event including step changes. Significantly rising or falling trends underlined.

1= 2004 Cochrane systematic reviews of clinical trials on corticosteroids and aciclovir or valaciclovir for Bell's palsy [3,4].

2= 2007 Scottish Bell's palsy study [5].

Final= percentage of patients treated for Bell's palsy at the end of the study period according to the categories of treatment.

Table 3. Untreated cases according to age and gender with results from multivariate logistic regression analysis.

Variable		Untreated (%)	Odds ratio (95%CI)	*P* value
Age group	16-30	913 (44.4)	-	
	30-39	1105 (47.0)	1.11 (0.99-1.25)	0.077
	40-49	1157 (46.0)	1.07 (0.95-1.20)	0.263
	50-59	1225 (47.6)	1.14 (1.01-1.28)	0.032
	60-69	1215 (50.4)	1.28 (1.13-1.44)	<0.001
	>70	1480 (58.0)	1.73 (1.54-1.94)	<0.001
Gender	Male	3459 (48.4)	-	
	Female	3636 (49.7)	1.04 (0.98-1.11)	0.231

FIGURE LEGENDS

Figure 1. Incidence of Bell's palsy in the UK from 2001 to 2012, standardised to the European standard population.

Error bars = 95% confidence intervals.

Figure 2. Management of Bell's palsy in the UK according to treatment.

Reference line: 1 = the 2004 Cochrane systematic reviews for Bell's palsy.

Reference line 2 = the 2007 SBPS.

Figure 3. Trends in referral to secondary care for Bell's palsy in the UK from 2001 to 2012.

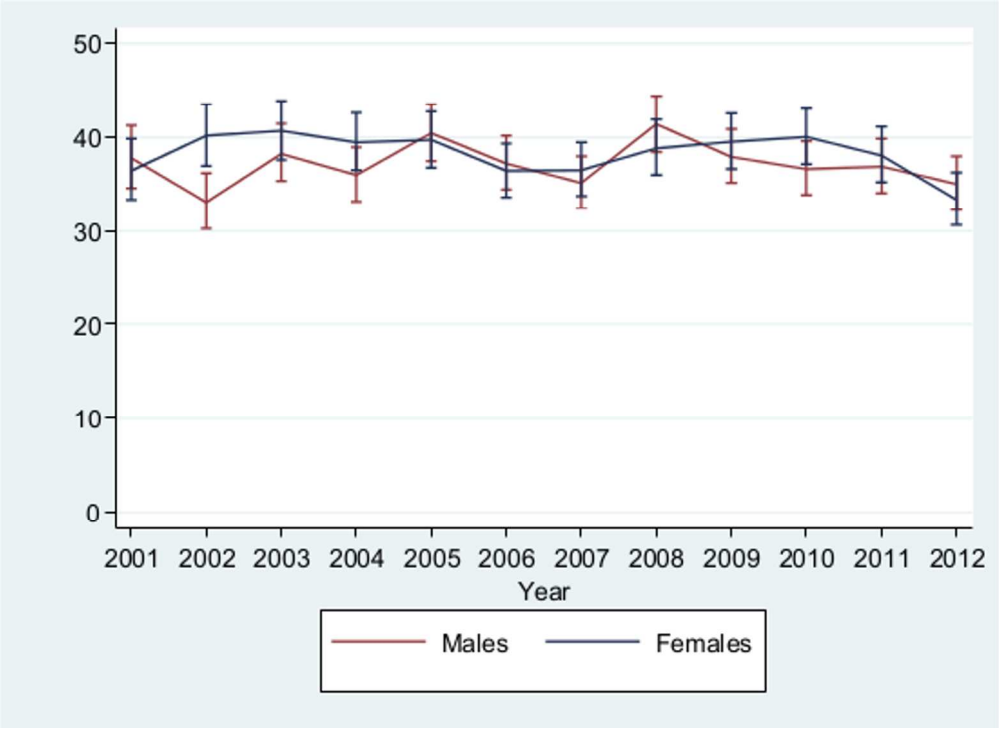

Figure 1. Incidence of Bell's palsy in the UK from 2001 to 2012, standardised to the European standard population.
Error bars = 95% confidence intervals.

173x125mm (300 x 300 DPI)

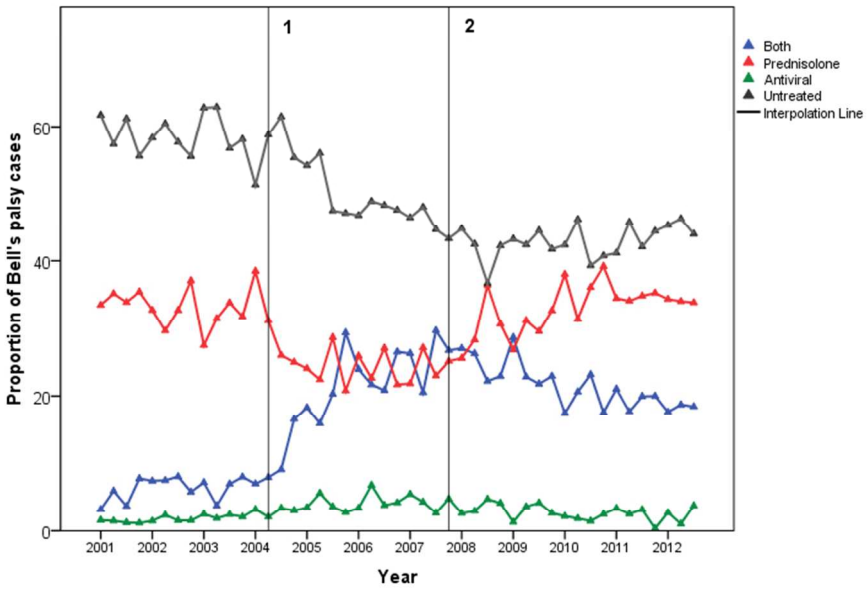

Figure 2. Management of Bell's palsy in the UK according to treatment.
Reference line: 1 = the 2004 Cochrane systematic reviews for Bell's palsy.
Reference line 2 = the 2007 SBPS.

288x190mm (72 x 72 DPI)

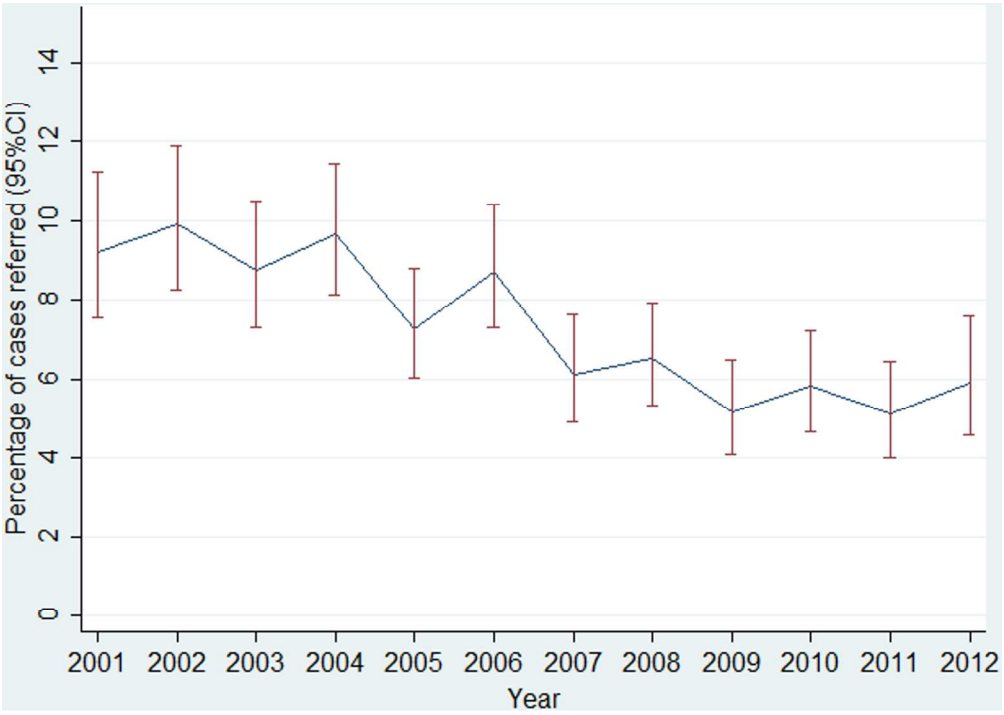

Figure 3. Trends in referral to secondary care for Bell's palsy in the UK from 2001 to 2012.
173x122mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page4
Methods			
Study design	4	Present key elements of study design early in the paper	Page5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page5-6
Bias	9	Describe any efforts to address potential sources of bias	Page5
Study size	10	Explain how the study size was arrived at	Page6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page6-7
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page7-8 Table 1
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1&3
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Page7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Table2

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Page7-8 Table2,3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Impact of clinical trial findings on Bell's palsy management in General Practice in the United Kingdom 2001-2012: interrupted time series regression analysis.

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ABSTRACT

Objectives: To measure the incidence of Bell's palsy and determine the impact of clinical trial findings on Bell's palsy management in the UK.

Design: Interrupted time series regression analysis and incidence measures.

Setting: General practices in the United Kingdom contributing to the Clinical Practice Research Datalink (CPRD).

Participants: Patients ≥16 years with a diagnosis of Bell's palsy between 2001 and 2012.

Interventions: 1) Publication of the 2004 Cochrane reviews of clinical trials on corticosteroids and antivirals for Bell's palsy which made no clear recommendation on their use, and 2) publication of the 2007 Scottish Bell's Palsy Study (SBPS) which made a clear recommendation that treatment with prednisolone alone improves chances for complete recovery.

Main Outcome Measures: Incidence of Bell's palsy per 100,000 person-years. Changes in the management of Bell's palsy with either: prednisolone therapy; antiviral therapy; combination therapy (prednisolone with antiviral therapy); or untreated cases.

Results: During the 12 year period 14,460 cases of Bell's palsy were identified with an overall incidence of 37.7 per 100,000 person-years. The 2004 Cochrane reviews were associated with: immediate falls in prednisolone therapy (-6.3% [-11.0 to -1.6]); rising trends in combination therapy (1.1% per quarter [0.5 to 1.7]); and falling trends for untreated cases (-0.8% per quarter [-1.4 to -0.3]). The SBPS was associated with: immediate increases in prednisolone therapy (5.1% [0.9 to 9.3]) and rising trends in prednisolone therapy (0.7% per quarter [0.4 to 1.2]); falling trends in combination therapy (-1.7% per quarter [-2.2 to -1.3]); and rising trends for untreated cases (1.2% per quarter [0.8 to 1.6]). Despite improvements 44.0% still remain untreated.

Conclusions: The SBPS was clearly associated with change in management but a significant proportion of patients failed to receive effective treatment which cannot be fully explained. Clarity and uncertainty in clinical trial recommendations may change clinical practice. However, better ways are needed to understand and circumvent barriers to implementing clinical trial findings.

Article focus

- What is the incidence of Bell's palsy in people aged 16 years onwards in the UK?
- What has been the impact of clinical trial findings on the management of Bell's palsy?

Key messages

- The incidence of Bell's palsy is 37.7 per 100,000 person years, higher than previously thought.
- Clinical trial findings were clearly associated with change in management
- A significant proportion of Bell's palsy cases still appear to be untreated.

Strengths

- This is the largest population based study evaluating Bell's palsy incidence and management
- The dataset used is of high quality and validated for use in research

Limitations

- Interrupted time series regression assess association rather than causation.
- The reasons for the high proportion of untreated cases remains largely unknown

INTRODUCTION

The foundations of medical evidence are based upon findings from clinical trials but their translation into clinical practice is an uncertain process and can be problematic.[1-3] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which demonstrated an increased risk of cardiovascular events with doxazosin compared to chlorthalidone, was associated with modest but limited reductions in alpha-blocker prescribing in the United States but no immediate impact in other countries.[4, 5] Several theoretical and practical barriers to achieve knowledge translation exist in implementation research and it has been suggested that multi-faceted approaches tailored to the intervention under review are superior to passive dissemination.[6] Two studies assessing the impact of implementing UK National Institute for Clinical Excellence (NICE) guidelines reported variable results suggesting that factors including professional experience, a stable evidence base and cost implications may all influence clinician behaviour.[7, 8] Similar results from a range of clinical settings have been found in other countries.[9-11]

Large population based studies measuring the incidence of Bell's palsy (acute idiopathic facial ~~paralysis~~palsy) are rare. ~~and p~~Currently published incidence rates of Bell's palsy are inconsistent, varying from as low as 11 per 100,000 to 51.9 per 100,000 person-years.[12-18] Part of this variation is related to heterogeneity in the method of case-detection and differences in diagnostic criteria used. In addition, not all published studies are large population based studies and variations in sampling technique may bias measures of disease occurrence. The incidence of Bell's palsy in the UK has been reported only once at 20.2 per 100,000 person-years.[18] However, this measure was based upon electronic health data at a time when electronic medical records (EMRs) were not as widespread or as well

integrated into clinical practice as they are now. Currently 97% of UK family doctors use EMRs.[19]

In 2007, the results of a large factorial randomized clinical trial examining the effectiveness of corticosteroids alone or in combination with antivirals for Bell's palsy was reported in the New England Journal of Medicine.[20] The Scottish Bell's Palsy Study (SBPS) clearly demonstrated that early treatment with prednisolone significantly improved the chance of complete recovery and that treatment with aciclovir conferred no additional benefit. The clinical trial received publicity from other medical journals, evidence-based collections and the general media, raising the profile of the article and helping to disseminate its recommendations.[21, 22] Prior to the SBPS recommendations on the effectiveness of corticosteroids and antivirals for Bell's palsy were unclear.[23, 24] In 2009, a Cochrane review of clinical trials for antivirals in Bell's palsy was published incorporating both the SBPS and data from a large Swedish clinical trial reporting similar findings.[25, 26] The need for high-quality research in this area was therefore demonstrated, large robust clinical trials were conducted, clear recommendations were made and results widely disseminated. In this regard, it would be reasonable to assume changes in clinical practice would then follow. Use of EMRs provides a valuable opportunity to evaluate the impact of clinical trials at a population level and provide robust measures of occurrence. We decided to evaluate the impact of clinical trial data on Bell's palsy management which has never been reported and determine the incidence of Bell's palsy over a twelve year period.

METHODS

The study was conducted using data from the Clinical Practice Research Datalink (CPRD) in the UK, formerly known as the General Practice Research Database.[27] CPRD is one of the world's largest longitudinal databases containing EMRs from over 640 UK general practices. CPRD contains electronic data about patient demographics, prescriptions, clinical events, medical diagnoses, hospital referrals, admissions and deaths. Medical diagnoses and clinical events are recorded using the Read code system of classification.[28] General practices are required to meet defined quality standards in order to contribute data to CPRD which is of high quality having been validated for use in research.[29, 30]

Study population

The study population consisted of all patients ≥16 years of age with an incident diagnosis of Bell's palsy occurring between 1st January 2001 and 30th September 2012. New Bell's palsy cases were defined by an incident Read code for Bell's palsy in patients with at least one year of up to standard medical history before the incident Read code for Bell's palsy. Incidence rates for Bell's palsy were calculated per year and for the overall study period. The numerator was the total number of new Bell's palsy cases recorded by general practitioners and the denominator was the number of person years of total population from contributing practices. Rates per 100,000 person-years were calculated by gender directly standardised to the European standard population.

Outcome

For each new Bell's palsy case, prescription data were used to define four different treatment categories consisting of: oral prednisolone therapy; oral antiviral therapy; oral prednisolone with antiviral (combined) therapy; and untreated. Treatments were defined by prescriptions occurring within seven days before and after ~~of~~ the date of diagnosis.

Antiviral therapy was defined by prescriptions for oral acyclovir, famciclovir or valaciclovir. The proportion of patients treated for Bell's palsy was measured per quarter stratified by treatment category. The denominator used was the total number of new Bell's palsy cases per quarter. Quarters were defined from the beginning of January 2001 (January, February and March) to the end of the third quarter of 2012. For ease of reference quarters are labelled 2001q1 to 2012q3. Referral to secondary care was determined by the presence of a referral code in the primary care records occurring within fourteen days of the date of diagnosis for specialities of: ear, nose and throat (ENT), ophthalmology and neurology. Referral codes were based upon the National Health Service (NHS) classification. Due to limited numbers of referrals, the proportion of Bell's palsy cases referred to secondary care was measured per year.

Events

Events were pre-specified according to publication of the 2004 Cochrane systematic reviews of clinical trials which made no clear recommendation on the use of corticosteroids and antivirals for Bell's palsy (2004q2) [23, 24] and the SBPS which made clear recommendations that treatment with prednisolone alone improved chances of complete recovery (2007q3).[20]

Statistical analysis

Interrupted time series for the specified outcomes were plotted and impact examined in a single segmented regression analysis model with parameters for the two events.[31] Key parameters for each event were estimated: a) the slope or trend in treatment before the event; b) the step change in treatment immediately following the event; and c) the change in trend from the pre-event trend. The presence of serial autocorrelation was tested for using the Durbin-Watson statistic with visual inspection of residuals plots. The minimum

number of data points between interventions was thirteen. Associations between untreated cases and the patient characteristics of age and gender were evaluated using multivariate binary logistic regression. Analysis was conducted using PASW Statistics v18 (IBM Software 2009) and STATAv11 (StataCorp. 2009).

RESULTS

Incidence of Bell's palsy

A total of 14,460 patients with incident Bell's palsy were identified (table 1). The overall incidence of Bell's palsy for the study period was 37.7 per 100,000 person-years. The incidence of Bell's palsy increased with age and was similar for gender. The annual standardised incidence of Bell's palsy remained fairly constant throughout the period of study (figure 1).

Effect of clinical trials on management

Time trends for the management of Bell's palsy are shown in figure 2. In 2001q1 Bell's palsy was treated with prednisolone only in 33.4% (95%CI 29.8-37.0); combined therapy in 5.1% (95%CI 1.7 to 8.5); antivirals only in 1.1% (95%CI -0.1 to 2.3); and was untreated in 60.4% (95%CI 57.1 to 63.8). The baseline trend was flat for all treatment categories i.e. there were no significant quarter to quarter changes in treatment (table 2). The 2004 Cochrane systematic reviews of clinical trials were associated with; a significant absolute step fall in treatment with prednisolone of -6.3% (95%CI -11.0 to -1.6) during 2004q2 without any significant change in trend; change from a flat to a significantly rising trend in treatment with combined therapy of 1.1% per quarter (95%CI 0.5 to 1.7); and change from a flat to a significantly falling trend in untreated patients (-0.8% per quarter [95%CI -1.4 to -0.3]).

The SBPS was associated with: a significant immediate step rise in treatment with prednisolone only of 5.1% (95%CI 0.9 to 9.3) followed by a rising trend of 0.7% per quarter (95%CI 0.4 to 1.2); change from a rising to a falling trend in treatment with combined therapy of -1.7% per quarter (95%CI -2.2 to -1.3); change from a falling to a rising trend in untreated patients (1.0% per quarter [95%CI 0.2 to 1.9]); and change to a falling trend in treatment with antivirals alone (-0.2% per quarter [95%CI -0.4 to -0.0]).

Untreated cases

The proportion of untreated Bell's palsy patients fell from 62% during the 12 year study period but remained at 44.0% at 2012q3. The proportion of untreated Bell's palsy patients was high across all age categories (range 44.4% to 58.0%, table 3) but was significantly greater in patients over the age of 60 years. The probability of being untreated was not significantly influenced by gender.

Referrals to secondary care

Of the 14,460 new Bell's palsy cases identified, a total of 1051 (7.3%, 95%CI 6.9 to 7.7) patients were referred to ENT, ophthalmology or neurology. More treated cases of Bell's palsy were referred to secondary care than untreated cases (9.2% [95%CI 8.5 to 9.9] for treated vs. 6.5% [95%CI 5.9 to 7.1] for untreated). The proportion of patients referred to secondary care fell during the study period (figure 3) ranging from 9.2% (95%CI 7.5 to 11.2) in the first quarter of 2001 to 5.9% (95%CI 4.6 to 7.6) in the third quarter of 2012 (difference 3.3%, 95%CI -0.1 to 6.6%).

DISCUSSION

Clinical trial findings are the cornerstone of medical evidence to judge the effectiveness of interventions but not all recommendations effectively translate into clinical practice. Evaluating changes in prescribing behaviour at a population level can support clinical trials in measuring their impact.

Impact of clinical trial evidence

The SBPS was associated with a significant clinical impact on Bell's palsy management by increasing treatment with corticosteroids and reducing combination therapy with antivirals based upon the results of time series regression analysis. ~~In this sense, u~~Use of ~~corticosteroids~~ prednisolone alone increased by ~~88~~70% from the point immediately before ~~the lowest point in 2005~~publication of the SBPS to the highest point in 2010. Conversely, combination therapy fell by 41% from the ~~highest~~ point ~~in 2007~~immediately before publication of the SBPS to the lowest point in 2010. Equally important however, uncertainty in recommendation or lack of evidence from clinical trials also appears to significantly influence clinical practice. This is highlighted by the 2004 reviews which were associated with an increase in combination therapy by 323% from the lowest point in 2004 to the highest point in 2007. There are several reasons why this may have occurred. Clinical uncertainties regarding effectiveness may have justified the use of antivirals with increasing pharmaceutical promotion. This would also indirectly promote corticosteroid use and help explain the falling trend in untreated patients. When no evidence for antivirals was found, promotion of combination therapy for Bell's palsy may have stopped, thus halting the falling trend in untreated patients. Corticosteroids being off-patent cheap drugs were unlikely to be marketed in the same way. Uncertainty in clinical management partly stems from uncertainty regarding aetiology. If a non-viral aetiology for Bell's palsy was confirmed, the

use of antiviral would be biologically implausible. Further work could usefully address the aetiology of Bell's palsy.

Adoption of clinical trial findings from the SBPS clearly occurred but was limited despite clear recommendations and subsequent dissemination. In this regard, a significant number of patients are still treated with antivirals and even more receive no effective treatment despite updated recommendations.[26, 32] In addition, there is a suggestion that the rising trend in prednisolone only therapy and falling trend in combination therapy over the last year of observation is plateauing, which may be an effect related to the time since publication. This may be related to conflicting recommendations for antiviral use appearing in the literature after the SBPS, especially in relation to severe cases.[33-35] These uncertainties make recommendations less likely to be adopted.[10] Relatively few studies have attempted to evaluate the impact of clinical trials on clinical practice. The ALLHAT trial was a large randomised double-blind trial in which the study doxazosin arm was terminated early due to an unfavourable risk of cardiovascular events compared to treatment with chlorthalidone. The ALLHAT trial was associated with a 26% reduction in annual alpha-blocker prescription orders, a 22% reduction in dispensed alpha-blocker prescriptions and a 54% reduction in physician reported alpha-blocker drug-use in the US.[4] Despite the clinically significant reductions, significant numbers of hypertensive patients still received treatment with alpha-blockade and it was proposed that further strategies are required to increase the impact clinical trial findings should have. Our study observed similar findings in that although a clinically significant impact occurred, clinical evidence was not fully adopted.

Untreated cases

Significant numbers of patients failed to receive effective therapy for Bell's palsy. Increasing age is associated with increasing co-morbidity, which may lead to relative contraindications to therapy. Although older patients had the greatest probability of being untreated, the proportion of untreated patients was high among all age categories with 44.4% of patients

under the age of 30 appearing to not receive any effective treatment by the end of the study period. It is therefore likely that relative contraindications to therapy as a result of co-morbidities would account for only a minority of untreated cases. In older patients, the main differential diagnosis of Bell's palsy is stroke which may have resulted in more patients receiving investigation and treatment from secondary care services. In this regard, cases may have presented to accident and emergency rather than primary care as a result of recommendations for rapid urgent assessment of suspected stroke potentially ~~leading to an~~ overestimating ~~in~~ the number of untreated patients in this age category. Conversely, concerns regarding a diagnosis of stroke may also lead to delayed diagnosis of Bell's palsy potentially missing the opportunity for early effective treatment with prednisolone therapy in these patients.

Incidence

The incidence of Bell's palsy was similar between genders, increased with age and remained fairly constant throughout the twelve year period. The incidence of Bell's palsy varies markedly throughout the literature with differences partly relating to the method of case-detection or diagnostic criteria used. Although the incidence of Bell's palsy in this study was greater than for others [14, 15, 17, 18] a large US study using electronic health surveillance data reported a similar incidence of 42.7 per 100,000 person-years.[16] Our study also reported similar increases in incidence with age found elsewhere.[16, 18]

Given the low rate of referrals to ENT, ophthalmology and neurology specialities (the main specialities patients with Bell's palsy would be referred to in the UK) it can be seen that primary care physicians diagnose and treat the great majority of cases. For the UK at least, primary care data are therefore a valuable source for measuring the incidence of Bell's palsy. Only one other study has reported incidence rates from the UK. Rowlands et al used

EMRs from 1992 to 1996 to estimate an incidence of 20 per 100,000 person-years, a figure significantly lower than ours.[18] It remains uncertain whether the incidence of Bell's palsy has truly increased or simply been measured more accurately. The previous study used data at a time when EMRs and established coding practices were not as widespread or as well integrated into clinical practice as they are now which may have led to an under-recording of cases. The fairly stable trend in incidence over a twelve year period from our study also makes it less likely that the incidence of Bell's palsy has increased over time.

Strengths and limitations

This is the largest population based study evaluating the incidence and management of Bell's palsy in adults. Bell's palsy may occur rarely in children however the vast majority of cases will occur in adults and increases substantially with age. Acute idiopathic facial palsy in children is more likely to be managed in secondary care, from which no prescribing data are available. As such, inclusion of patients assessing the impact of clinical trial data would be to underestimate the impact of clinical trial findings. Perhaps of greater importance however lies in demonstrating the impact of clinical trials on Bell's palsy management, which has never been reported potentially having wider implications. Cochrane systematic reviews are considered a gold standard for summaries of evidence-based healthcare in the UK and internationally because of the rigorous approach in combining high-standard medical research. For this reason the Cochrane systematic reviews of clinical trials were evaluated especially as changes in recommendation occurred during the study period. In the UK, patients register with general practices in order to access free healthcare from the NHS. Most prescriptions, including those recommended from secondary care, are issued electronically from general practice making UK EMRs a valuable tool for research. Bell's palsy cases were diagnosed by family physicians in real life settings and no scale was used to

quantify the degree of facial nerve dysfunction. We are unable to ascertain whether or not the diagnosis of Bell's palsy was recorded at initial presentation or following complete investigation. For this reason, we included prescriptions issued within a seven day period before and after the date of Bell's palsy recording. Some patients may have received treatment from other sources (e.g. accident and emergency units) with potential overestimation of untreated patients. However, this is likely to be a minority of patients due to the culture of healthcare provision in the UK and the size and quality of the database used. Although it would appear from the low rate of referrals to ophthalmology, ENT and neurology that Bell's palsy is primarily managed in primary care, we cannot exclude the possibility that patients were referred to other disciplines potentially underestimating the number of referrals. Time series regression assesses association rather than causation but remains a strong design for estimating the effects of interventions in non-randomized settings.[29] Despite this, we cannot exclude the possibility that other events may have occurred which influenced the findings.

Clinical implications

A large proportion of patients do not appear to receive any effective treatment for their condition. Although ~~most~~ the majority of Bell's palsy cases will resolve spontaneously, full recovery is more likely and quicker in those treated with prednisolone.[20,36] This is important as around 30% of untreated patients will suffer long term problems including facial disfigurement potentially complicated by facial contracture, reduced sense of taste, speech problems, eye-mouth synkinesias, corneal ulceration and adverse psychological impact. Clearly, any treatment which reduces the risk of long-term complications and speeds up recovery should be considered. Therefore, more people should be offered early treatment with corticosteroids for Bell's palsy. More broadly, there is a societal need in

health care research to better evaluate the impact of large clinical trials and not to assume that knowledge translation naturally occurs via passive dissemination. More work is therefore needed to understand and circumvent the barriers to adoption of clinical trial evidence. In conclusion, clinical trial findings had a clear impact on primary care management of Bell's palsy but a significant proportion of patients failed to receive effective treatment. Clinical trials making clear recommendations can be associated with changes to clinical practice, but their impact may still be limited. Conversely, lack of evidence or uncertain clinical trial recommendations may also be associated with changes in clinical practice. Better ways are needed to circumvent the barriers to implementing clinical trial results.

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Data sharing: Descriptive statistics for Bell's palsy cases are available from the corresponding author.

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TABLES

Table 1. Incidence of Bell's palsy (per 100,000 person-years) by age and gender.

Age (years)	Male		Female		Overall Incidence
	No. (%)	Incidence*	No. (%)	Incidence*	
16-30	949 (46.2)	24.0	1107 (53.8)	30.3	27.0
30-39	1155 (49.2)	33.6	1194 (50.8)	35.6	34.5
40-49	1313 (52.2)	34.4	1202 (47.8)	32.5	33.4
50-59	1341 (52.0)	40.0	1237 (48.0)	37.6	38.8
60-69	1229 (51.0)	45.9	1180 (49.0)	42.9	44.4
≥70	1154 (45.2)	66.6	1399 (54.8)	68.2	67.4

Table 2. Quarterly time series regression analysis of Bell's palsy treatment from 2001 to 2012.

Event	Segments*	Untreated % (95% CI)	Prednisolone % (95% CI)	Combination % (95% CI)	Antiviral % (95% CI)
Baseline	2001q1 (intercept)	60.43 (57.10 to 63.78)	33.39 (29.79 to 36.99)	5.10 (1.78 to 8.42)	1.09 (-0.09 to 2.26)
1	2001q1 to 2004q1	-0.28 (-0.69 to 0.13)	-0.01 (-0.47 to 0.44)	0.18 (-0.24 to 0.60)	0.11 (-0.04 to 0.27)
	20004q2 step change	2.15 (-2.15 to 6.44)	-6.32 (-11.03 to -1.60)	3.61 (-0.74 to 7.96)	0.57 (-1.05 to 2.18)
	2004q2 to 2007q3	-0.81 (-1.36 to -0.25)	-0.27 (-0.88 to 0.34)	1.09 (0.53 to 1.65)	-0.01 (-0.22 to 0.20)
2	2007q4 step change	-2.13 (-5.96 to 1.70)	5.10 (0.90 to 9.31)	-2.17 (-6.05 to 1.72)	-0.81 (-2.25 to 0.63)
	2007q4 to 20012q3	1.22 (0.79 to 1.64)	0.71 (0.41 to 1.18)	-1.73 (-2.17 to -1.30)	-0.19 (-0.35 to -0.03)
Final	2012q3	43.98 (38.02 to 49.94)	33.83 (28.15 to 39.51)	18.42 (13.76 to 23.08)	3.76 (1.47 to 6.05)

*Trend in prescribing before and after the event including step changes. Significantly rising or falling trends underlined.

1= 2004 Cochrane systematic reviews of clinical trials on corticosteroids and aciclovir or valaciclovir for Bell's palsy [3,4].

2= 2007 Scottish Bell's palsy study [5].

Final= percentage of patients treated for Bell's palsy at the end of the study period according to the categories of treatment.

Table 3. Untreated cases according to age and gender with results from multivariate logistic regression analysis.

Variable		Untreated (%)	Odds ratio (95%CI)	*P* value
Age group	16-30	913 (44.4)	-	
	30-39	1105 (47.0)	1.11 (0.99-1.25)	0.077
	40-49	1157 (46.0)	1.07 (0.95-1.20)	0.263
	50-59	1225 (47.6)	1.14 (1.01-1.28)	0.032
	60-69	1215 (50.4)	1.28 (1.13-1.44)	<0.001
	>70	1480 (58.0)	1.73 (1.54-1.94)	<0.001
Gender	Male	3459 (48.4)	-	
	Female	3636 (49.7)	1.04 (0.98-1.11)	0.231

FIGURE LEGENDS

Figure 1. Incidence of Bell's palsy in the UK from 2001 to 2012, standardised to the European standard population.

Error bars = 95% confidence intervals.

Figure 2. Management of Bell's palsy in the UK according to treatment.

Reference line: 1 = the 2004 Cochrane systematic reviews for Bell's palsy.

Reference line 2 = the 2007 SBPS.

Figure 3. Trends in referral to secondary care for Bell's palsy in the UK from 2001 to 2012.